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(54) Title: THIAZOLIDINE AND OXAZOLIDINE DERIVATIVES FOR THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION AND INHIBITION OF CARDIOMYOCYTE APOPTOSIS

(57) Abstract

It has been demonstrated that antidiabetic thiazolidine and oxazolidine derivatives (glitazones) exhibit novel effects on apoptosis of cardiomyocytes. These substances are capable of greatly decreasing apoptosis by a pathway that is not Caspase 3 dependent. Addition of IGF1 to the treatment further prevents apoptosis. Glitazones alone or glitazones plus IGF1 should be administered at the beginning of a myocardial infarction and continued through the recuperation period to reduce morbidity and prevent unfavorable remodeling of the myocardium.

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THIAZOLIDINE AND OXAZOLIDINE DERIVATIVES FOR THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION AND INHIBITION OF CARDIOMYOCYTE APOPTOSIS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present application concerns cardiology and more specifically pharmacological treatments for myocardial infarctions.

2. Description of Related Art

Acute myocardial infarction is associated with adverse remodeling of the myocardium and subsequent high mortality. The short-term or long-term prognosis after acute myocardial infarction is related to the amount of myocardium damaged and thus to the extent of left ventricular dysfuncion. Two forms of cardiac muscle cell death occurs during and after acute myocardial infarction—**necrosis** and **apoptosis**. The most effective way to limit myocardial necrosis in evolving myocardial infarction may be early restoration of coronary blood flow. In a high proportion of patients, myocardial infarction is associated with thrombotic occlusion of a coronary artery. The ability to restore blood flow to ischemic myocardium, notably with intravenous administration of thrombolytic agents such as streptokinase

or tissue plasminogen activator, has heightened clinical interest both in the underlying processes of myocardial ischemic injury and in the consequences of reperfusion because early reperfusion during acute myocardial infarction represents an effective means to limit tissue necrosis and preserve myocardial function. Ultimately, it is the cellular mechanisms of ischemia that determine the full extent of an infarct and the success of therapy, and while timely reperfusion can salvage ischemic myocardium, in some circumstances it may itself cause cellular damage.

Reperfusion associated damage or myocardial stunning is generally believed to be mediated in part by reactive oxygen species. A longer period of ischemia results in irreversible cell injury where the extent of tissue necrosis is related to the severity and duration of the ischemic episode. There is ample evidence to suggest that reoxygenation of the ischemic myocardium is accompanied by free radical generation from a variety of intracellular and/or extracellular sources, and that oxygen-derived free radicals may contribute to tissue injury. Superoxide dismutase (SOD) was the first antioxidant or free radical scavenger to undergo clinical trials for treatment of acute myocardial infarction. However, the efficacy of SOD in experimental models is controversial and may be attributed to lack of sustained beneficial effect due to short treatment period and short half-life of human recombinant or bovine erythrocyte SOD.

A number of agents have been described which exhibit beneficial effects in experimental models of myocardial stunning, including the antioxidant cyanidanol, the iron chelator 1,2-dimethyl-3-hydroxy-4-pyridone and a series of imidazol-2-thiones. Agents which inhibit functional responses of neutrophils, thromboxane synthetase or act as thromboxane receptor antagonists also exhibit beneficial effect in experimental models of myocardial ischemia.

Since adult cardiac muscle cells rarely proliferate, necrosis and apoptosis of cardiac muscle lead to permanent loss of cardiac muscle functioning units.

Apoptosis of cardiac muscle cells occurs following acute myocardial infarction and contributes to the extension of myocardial infarction and remodeling of myocardium. Since extension of myocardial infarction and myocardial remodeling leads to poor myocardial function and increased risk of heart failure, preventing myocardial apoptosis is expected to result in better myocardial function after myocardial infarction. Currently, no treatment specifically targeted against cardiac muscle apoptosis is available to patients suffering from heart disease is known to be available.

SUMMARY OF THE INVENTION

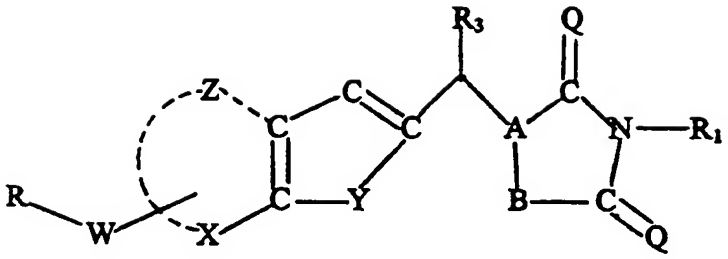
I have found that the antidiabetic thiazolidine and oxazolidine compounds can be used to improve myocardial remodeling and cardiac function after acute myocardial infarction. The discovery of a new use for these widely studied class of drugs will provide a new therapeutic approach for myocardial infarction since these drugs may be administered through oral, nasal, intravenous or pulmonary routes at the onset of myocardial infarction.

I have discovered a series of thiazolidine and oxazolidine derivatives which may be used for the treatment of acute myocardial infarction. These thiazolidine and oxazolidine derivatives are known to not only reduce insulin resistance but also to improve glucose intolerance, and to exhibit activity against obesity associated hypertension and anti-atherosclerotic activity. Now, I have unexpectedly and surprisingly found that these compounds are also effective in preventing apoptosis of cardiac muscle and in turn improve myocardial remodeling and cardiac function after acute myocardial infarction.

The compounds which comprise the pharmaceutical agents of this invention are known compounds and are used as antidiabetic compounds which lower the

concentration of glucose and lipids in blood. Representative compounds are disclosed in the following references: U.S. Pat. Nos. 5,708,012, 5,688,823, 5,614,542, 5,602,133, 5,578,620, 5,498,621, 5,478,852, 5,478,851, 5,441,971, 5,436,257, 5,356,913, 5,330,998, 5,266,582, 5,223,522, 5,132,317, 5,130,379, 5,120,754, 5,089,514, 5,061,717, 5,053,420, 5,037,842, 5,036,079, 4,968,707, 4,918,091, 4,873,255, 4,812,570, 4,791,125, 4,775,687, 4,738,972, 4,725,610, 4,703,052, 4,687,777, 4,572,912, 4,486,594, 4,461,902, 4,444,779, 4,438,141, 4,430,337, 4,340,605, 4,287,200 and European Pat. No. 0277,836, which are hereby incorporated by reference. Thiazolidine compounds related to those described herein have been disclosed in U.S. Patent Nos. 5,719,188, 5,614,542, 5,436,257, 5,356,913 and 5,053420 to have anti-hypertensive activity and have been found to be especially useful in the treatment and prophylaxis of hypertension associated with obesity. Thiazolidine compounds have also been described as anti-atherosclerosis agents in U.S. Pat. No. 4,791,125 mentioned above. However, none of the references have described these compounds as having an effect on cardiomyocyte apoptosis and/or myocardial remodeling following infarction.

The present invention provides a method for the improvement of myocardial remodeling and cardiac function after acute myocardial infarction in a mammal, which may be human, which method comprises administering to said mammal an effective amount of an agent selected from the group consisting of thiazolidine and oxazolidine derivatives having the formula (I),



(I)

wherein,

Q is O (oxo) or NOR_2 (imino), where R_2 is independently selected from hydrogen, alkyl, cycloalkyl, or acyl; R_1 is hydrogen, alkyl, cycloalkyl, alkoxycarbonyl, or carboxyalkyl and their ester derivatives; R_3 is hydrogen, alkyl or cycloalkyl.

B is O (oxa) or S (thia); and A is N or CR_4, where R_4 is hydrogen, cycloalkyl or alkyl; R_3 and R_4 may combine to form a cyclic ring, optionally substituted with one or more groups selected from oxo, alkyl, hydroxy or acyloxy groups on the cyclic ring; one or more ring methylene carbons optionally substituted by an atom selected from oxygen or nitrogen to afford heterocyclic ring structure; R_3 and R_4 may combine to form a double bond.

Y is CH=CH, N=CH, CH=N, S, O or NR_5, where R_5 is selected from hydrogen, cycloalkyl or alkyl. The ring carbons may be additionally substituted with one or more groups selected from halogens, alkyl, haloalkyl, hydroxy, alkoxy or acyloxy.

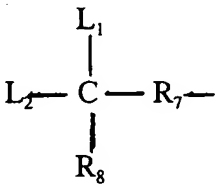
X is O (oxa), C=O (carbonyl), CHOH, CH_2, $C=NOR_2$, S, SO, SO_2, SO_2NR_5, R_5NSO_2, $CONR_5$ or NR_5CO, where R_5, as described earlier, is hydrogen, cycloalkyl or alkyl.

Z is CH=CH, CH=N, -(CH_2)nO- or (CH_2)n, where n is 1-3, or " no bond " i.e. X is directly bonded to W.

W is (CH-R_6)m, where m is 0-4, R_6 is H, alkyl, cycloalkyl, hydroxy, (CH_2)nOH and their acyl derivatives; n is 1-3 as defined earlier; or a 5- or 6-membered saturated nitrogen heterocycle such as pyrrolidine or piperidine, wherein the methylene hydrogens are optionally substituted by alkyl and hydroxy groups and the R group is attached to the nitrogen heteroatom of the heterocyclic ring.

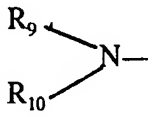
R is structurally diverse variable comprised of the several compositions detailed as follows. The thiazolidine and oxazolidine derivatives may further be selected from compounds wherein

R is of the formula (II),



(II)

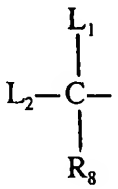
wherein R_8 is alkyl, cycloalkyl, aralkyl, aryl, a five- to ten-membered heterocyclic group including one or two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, or a group of the formula



where R_9 and R_{10} are the same or different and each represents an alkyl, aralkyl or heterocyclyl or R_9 and R_{10} are combined with each other either directly or as interrupted by a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur to form a five- or six-membered ring as taken together with the nitrogen atom adjacent to R_9 and R_{10}; R_7 is a bond or lower alkylene group; L_1 and L_2 may be the same or different and each is lower alkyl or L_1 and L_2 are combined with each

other to form an alkylene group, provided that when R_8 is other than alkyl, L_1 and L_2 may further be hydrogen, respectively.

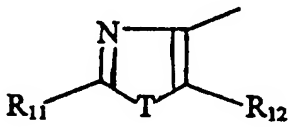
When R_7 repesents a bond, the compound of formula (II) is represented by the following formula (III),



(III)

Thus, when R_7 is a bond, the atoms adjacent thereto on both sides are directly combined together.

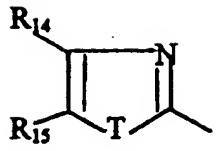
The thiazolidine and oxazolidine derivatives may further be selected from compounds wherein R is of the formula (IV),



(IV)

wherein T is O, S or NR_{13}; R_{13} is hydrogen or alkyl; R_{11} is hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl or mono- or disubstituted aryl with the same or different groups which are alkyl, alkoxy, haloalkyl, hydroxy, acyloxy or halogens; R_{12} is hydrogen or an alkyl group which may be substituted by a hydroxy or acyloxy group.

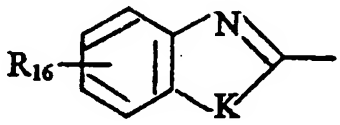
The thiazolidine and oxazolidine derivatives may further be selected from compounds where R is of the formula (V),



(V)

wherein T is O, S and NR_{13} as defined above; R_{14} and R_{15} each independently is hydrogen, cycloalkyl, alkyl, aryl, aralkyl or a heterocyclic residue which may optionally be substituted and R_{14} and R_{15} may jointly, together with the oxazole, thiazole or imidazole ring, form a condensed ring.

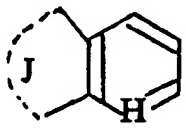
The thiazolidine and oxazolidine derivatives may be further selected from compounds where R represents any of the following groups:



(VIa)

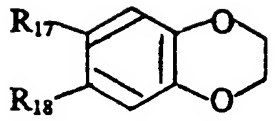
wherein K represents a sulfur or oxygen atom or an NH group which is either unsubstituted or substituted by an alkyl group;

R_{16} represents a hydrogen or halogen atom or an alkyl group or an alkoxy group or haloalkyl or cyano group;



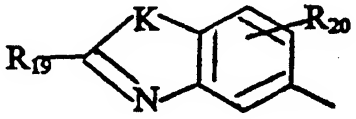
(VIb)

wherein J represents an unsaturated or partially or completely saturated ring with 5 or 6 members and H represents CH or N;



(VIc)

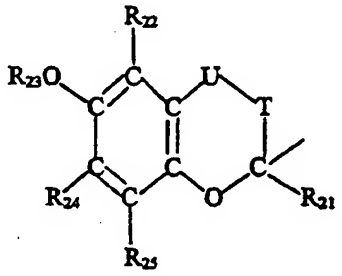
wherein R_{17} and R_{18}, which are identical or different, represent a hydrogen atom, a halogen atom, alkyl group, alkoxy group, or together form with the carbon atoms to which they are attached a saturated ring with 5 or 6 members which may optionally contain 1 or 2 oxygen atoms;



(VId)

wherein R_{19} is alkyl, cycloalkyl, heterocyclyl, aryl or substituted aryl with one or more substituents, selected from alkyl, alkoxy, haloalkyl, halogens, hydroxy and acyloxy groups; R_{20} is hydrogen, alkyl, alkoxy, halogen and K is as defined above for structure (VIa);

The thiazolidine and oxazolidine derivative may be further selected from compounds where R is of formula (VII),



(VII)

wherein:

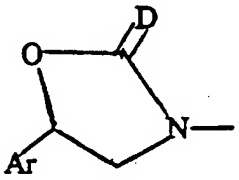
R_{21} and R_{22} are the same or different and each represents hydrogen or alkyl; R_{23} represents hydrogen, alkyl, an acyl group, alkoxycarbonyl group or an

aralkyloxycarbonyl group; R_{24} and R_{25} are the same or different and each represents hydrogen, alkyl or alkoxy or R_{24} and R_{25} together represent an alkylenedioxy group, wherein the alkylene portion is methylene and ethylene.

U represents a methylene group, a carbonyl group, a group of formula $>CH\text{-}OR_{26}$, where R_{26} represents any one of the atoms or groups defined for R_{23} and may be the same as or different from R_{23}, or a group of formula $>C=N\text{-}OR_{27}$, where R_{27} represents hydrogen or alkyl;

T represents a single bond or a methylene group; or when U represents a carbonyl group or said group of formula $>C=N\text{-}OR_{27}$, T, R_{21} and the carbon atom to which R_{21} is attached may together represent a group of formula $-CH=C<$; or U-T may represent a carbon-carbon double bond;

The thiazolidine and oxazolidine derivatives may further be selected from compounds wherein R is of formula (VIII),



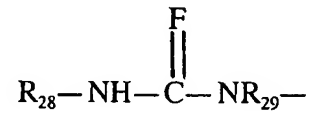
(VIII)

wherein D is O or S;

Ar represents an unsubstituted aryl group having from 4 to 10 ring carbon atoms or a substituted aryl group which has from 4 to 10 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents (a); said substituents (a) are selected from the group consisting of: halogen atoms; haloalkyl groups, in which the alkyl part has from 1 to 4 carbon atoms; hydroxy groups; acyloxy groups, in which the alkyl part has from 1 to 4

carbon atoms; alkyl groups having from 1 to 4 carbon atoms; and alkoxy groups having from 1 to 4 carbon atoms.

The thiazolidine and oxazolidine derivatives f—f may further be selected from compounds wherein R is of formula IX,

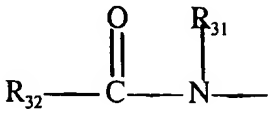


(IX)

wherein,

R_{28} represents an alkyl group or a substituted or unsubstituted aryl group; R_{29} represents hydrogen or alkyl; and F represents oxygen, sulfur or a moiety NR_{30} wherein R_{30} represents hydrogen or alkyl.

The thiazolidine and oxazolidine derivatives may further be selected from compounds wherein R is of formula X,



(X)

wherein,

R_{31} represents a hydrogen atom, an alkyl group, an aralkyl group wherein the alkyl or the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; R_{32} represents an alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aryloxy group, an aralkyl group, an aralkyl group wherein the alkylene or aryl moiety may be substituted or unsubstituted or a substituted or unsubstituted aromatic heterocyclyl group; or R_{31} together with R_{32} represents substituted or unsubstituted C_{3-4} polymethylene group,

optional substituents for the polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group.

The thiazolidine and oxazolidine derivatives may further be selected from compounds wherein R is of formula XI,

$$R_{33}—P— \qquad (XI)$$

wherein,

R_{33} represents a substituted or unsubstituted aryl group; P represents O, S, NR_{34} wherein R_{34} represents a hydrogen atom, an alkyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group.

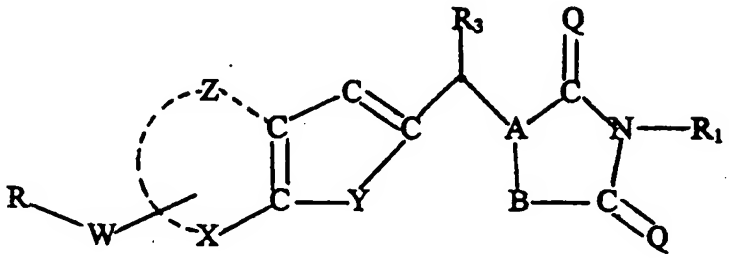
DETAILED DESCRIPTION

OF THE PREFERRED EMBODIMENTS

The following description is provided to enable any person skilled in the art to make and use the invention and sets forth the best modes contemplated by the inventor of carrying out his invention. Various modifications, however, will remain readily apparent to those skilled in the art, since the general principles of the present invention have been defined herein specifically to provide thiazolidine and oxazolidine derivative useful for treatment of myocardial infarction and control of cardiomyocyte apoptosis.

The present invention provides a method for the improvement of myocardial remodeling and cardiac function after acute myocardial infarction in a mammal, which may be human, which method comprises administering to said mammal an

effective amount of an agent selected from the group consisting of thiazolidine and oxazolidine derivatives having the formula (I),



(I)

wherein,

Q is O (oxo) or NOR_2 (imino), where R_2 is independently selected from hydrogen, alkyl, cycloalkyl, or acyl.

R_1 is hydrogen, alkyl, cycloalkyl, alkoxycarbonyl, or carboxyalkyl and their ester derivatives.

R_3 is hydrogen, alkyl or cycloalkyl.

B is O (oxa) or S (thia).

and A is N or CR_4, where R_4 is hydrogen, cycloalkyl or alkyl; R_3 and R_4 may combine to form a cyclic ring, optionally substituted with one or more groups selected from oxo, alkyl, hydroxy or acyloxy groups on the cyclic ring; one or more ring methylene carbons optionally substituted by an atom selected from oxygen or nitrogen to afford heterocyclic ring structure; R_3 and R_4 may combine to form a doublebond.

Y is CH=CH, N=CH, CH=N, S, O or NR_5, where R_5 is selected from hydrogen, cycloalkyl or alkyl. The ring carbons may be additionally substituted with one or more groups selected from halogens, alkyl, haloalkyl, hydroxy, alkoxy or acyloxy.

X is O (oxa), C=O (carbonyl), CHOH, CH_2, $C=NOR_2$, S, SO, SO_2, SO_2NR_5, R_5NSO_2, $CONR_5$ or NR_5CO, where R_5, as described earlier, is hydrogen, cycloalkyl or alkyl.

Z is CH=CH, CH=N, -(CH_2)nO- or (CH_2)n, where n is 1-3, or " no bond " i.e. X is directly bonded to W.

W is $(CH\text{-}R_6)$m, where m is 0-4, R_6 is H, alkyl, cycloalkyl, hydroxy, (CH_2)nOH and their acyl derivatives; n is 1-3 as defined earlier; or a 5- or 6-membered saturated nitrogen heterocycle such as pyrrolidine or piperidine, wherein the methylene hydrogens are optionally substituted by alkyl and hydroxy groups and the R group is attached to the nitrogen heteroatom of the heterocyclic ring.

In the compounds of the present invention, where R_1-R_6, R_8-R_{25}, R_{29}-R_{32} and R_{34} represent an alkyl group, this may be a straight or branched chain alkyl group having from 1 to 10 carbon atoms. Examples of such alkyl groups include the methyl, ethyl, propyl, 2-propyl, butyl, 2-methylpropyl, 2-butyl, 2-methyl-2-propyl, pentyl, 2-pentyl, 3-pentyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethyipropyl, hexyl, 2-hexyl, 3-hexyl, 2-methyl-pentyl, 3-methylpentyl, 4-methylpentyl, 1, 1-dimethyl-butyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethy1butyl, 1,1,2-trimethylpropyl, 1 ,2 ,2-trimethylpropyl, heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 3,3-dimethylpentyl, octyl, 1-methylheptyl, 2-ethylhexyl, 1, 1,3,3-tetramethylbutyl and decyl groups. When R_1-R_6, R_8-R_{25}, R_{29}-R_{32} and R_{34} represent an alkyl group, this is preferably a straight or branched chain alkyl group having from 1 to 8 carbon atoms, more preferably a straight or branched chain alkyl group having from 1 to 6 carbon atoms, and most preferably, this is a straight or branched chain alkyl group having from 1 to 4 carbon atoms, particularly the methyl or ethyl group.

In the compounds of the present invention, where R_1-R_6, R_8, R_{11}, R_{14}, R_{15} and R_{19} represent a cycloalkyl group, this may be a cycloalkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl.

In the compounds of the present invention, where R_{11}, R_{14}, R_{15}, R_{19}, R_{28}, R_{31}-R_{34} represent an aryl group, this may be an aryl group having from 6 to 10 carbon atoms; this is preferably an aryl group having from 6 or 10 carbon atoms; more preferably a phenyl, 1-naphthyl or 2-naphthyl group; and still more preferably a phenyl or 2-naphthyl group. Where such aryl group or Ar represents a substituted aryl group which is substituted with at least one substituent selected from the group consisting of substituents (a), this aryl group is preferably substituted with from one to five of said substituents, and more preferably with from one to three of said substituents. When more than one substituent is present on the aryl group, these substituents may be the same or different.

Where substituent (a) represents an alkyl group, this may be a straight or branched chain alkyl group having from 1 to 4 carbon atoms. Examples of such groups include methyl, ethyl, propyl, 2-propyl, 2-methylpropyl, 2-methyl-2-propyl, butyl and 2-butyl groups.

Where substituent (a) represents an alkoxy group, this may be a straight or branched chain alkoxy group having from 1 to 4 carbon atoms. Examples of such groups include: the methoxy, ethoxy, propoxy, 2-propoxy, 2-methylpropoxy, 2-methyl-2-propoxy, butoxy and 2-butoxy groups.

Where substituent (a) represents a haloalkyl group, the alkyl component may be straight or branched chain and has from 1 to 4 carbon atoms, particularly 1 or 2 carbon atoms, and preferably has from 1 to 3 halogen atoms which may be the same or different. Examples of such haloalkyl groups include the trifluoromethyl, trichloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 2-fluoroethyl, 2,2-dibromoethyl, 3-

chloropropyl, 3,3,3-trilluoropropyl and 4-fluorobutyl groups, of which alkyl groups having from 1 to 3 carbon atoms substituted by from 1 to 3 halogen atoms (and, where there are 2 or 3 halogen atoms, these are the same)are preferred, even more preferred are methyl or ethyl groups substituted by from 1 to 3 fluorine or chlorine atoms; the most preferred specific group is the trifluoromethyl group.

Where substituent (a) represents a halogen atom, this may be a fluorine, chlorine, bromine or iodine atom, preferably a fluorine or chlorine atom.

Where substituent (a) represents an acyloxy group, the alkyl component may be straight or branched chain and has from 1 to 4 carbon atoms. Examples of such acyloxy groups include acetyloxy, propionyloxy and 2,2,2-trimethylacetyloxy.

Examples of the aryl group or Ar when this is a C_6-C_{10} aryl group substituted with from 1 to 5 substituents (a), which substituents may be the same or different, include: the 2-chlorophenyl, 3-chlorophenyl, 3-(2-methyl-2-propyl)phenyl, 3-(2-propyl)phenyl, 3-ethylphenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 3,5-dichlorophenyl, 2,6-difluorophenyl, 2-chloro-4-fluorophenyl, 2-chloro-6-fluorophenyl, 3-chloro-4-fluorophenyl, 3-bromophenyl, 4-fluorophenyl, 3-fluorophenyl, 2-fluorophenyl, 3-methylphenyl, 4-(2-propyl)phenyl, 3-methoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3,5-dimethoxyphenyl, 2,5-dimethoxyphenyl, 3,4,6-trimethylphenyl, 3-fluoro-4-methoxyphenyl, 3-methyl-4-methoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 3,4-diethoxyphenyl, 2,5-dimethyl-4- methoxyphenyl, 3,5-dimethyl-4-hydroxyphenyl, 3,5-di-(2-methyl-2-propyl)-4-hydroxyphenyl, 5-bromo-2-ethoxyphenyl, 3,4,5-trimethoxyphenyl, 2,4,5-trimethoxyphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2,5-dimethoxy-3,4,6-trimethylphenyl and 2-methoxy-1-naphthyl group.

In the compounds of the present invention, where R_8-R_{10}, R_{14}, R_{15}, R_{31}, R_{32} and R_{34} represent an aralkyl group, in which the alkyl part has from 1 to 3 carbon atoms and the aryl part is a carbocyclic aromatic group having from 6 to 14 carbon

atoms, which may be substituted or unsubstituted and, if substituted, has at least one of substituents (a) defined and exemplified above, although the unsubstituted groups are preferred; in general, we prefer those aralkyl groups having a total of from 7 to 9 carbon atoms; examples of such aralkyl groups include the benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, l-naphthylmethyl, 2-naphthylmethyl, 2-(l-naphthylethyl, 2-(2-naphthyl)ethyl, benzhydryl (i.e. diphenylmethyl), triphenylmethyl, bis(o-nitrophenyl)methyl, 9-anthrylmethyl, 2,4,6-trimethylbenzyl, 4-bromobenzyl, 2-nitrobenzyl, 4-nitrobenzyl, 3-nitrobenzyl and 4-methoxybenzyl groups. It is also understood that phenyl cycloalkyl groups of 7 to 11 carbon atoms such as phenyl cyclopropyl are included.

In the compounds of the present invention, where R_8, R_{11}, R_{14}, R_{15}, R_{19} and R_{32} represent a heterocyclic group, this may be a heterocyclic compound with 5 to 10 carbon atoms and having 1 to 4 heteroatoms selected from O, S, NH and N-alkyl, where alkyl is as described earlier. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, pyrazolyl, pyridyl, indolyl, oxazolyl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, morpholinyl, piperidinyl, benzoxazolyl, benzothiazolyl and purinyl, such as adenylyl, which may be optionally substituted with one or more substituents selected from substituents (a) described above.

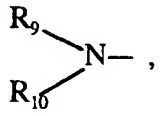
In the compounds of the present invention, where Z , W and R_1 (carboxyalkyl) represent an alkylene or substituted alkylene groups, this may be a straight or branched chain alkylene group having from 0 to 6 carbon atoms, and preferably from 0 to 4 carbon atoms. Examples of such alkylene groups include: the methylene, ethylene, ethylidene, trimethylene, propylidene, 1-methylethylene, 2-methylethylene, tetramethylene, 1-methyltrirnethylene, 2-metliyltrimethylene, 3-methyltrimethylene, isopropylidene, 1,2-dimethylethy lene, 1-ethylethylene, 2-ethylethylene, pentamethylene, l-methyltetramethylene, 2-methyltetramethylene, 1,2-dimethyltrirnethylene, 1,3~dimethyltrimethylene, 2,2-dimethyltrimethylene, l-

methyl-2~thylethylene, 1,2,2-trirnethylethylene, 1-propylethylene, hexamethylene, l-methylpentamethylene, 2-methylpentainethylene, 3-methylpentarnethylene, 5-methylpentamethylene, 1,2-dimethyltetrarnethylene, 1,3-dimethyltetramethylene, 1,4-dimethyltetramethylene, 1-ethyltetramethylene, 2-ethyltetramethylene, l-methyl-2-ethyltrimethylene, 2-methyl-2~thyltrimethylene, 2-propyltrimethylene, 1,1-diethylethylene, 1,2-diethylethylene or 1-methyl-2-propylethylene groups.

In the compounds of the present invention, where R_1 represents a carboxyalkyl group, the compounds of the present invention necessarily contain a carboxy group. These compounds are acids and can thus form salts and esters. The alkyl esters, especially those in which the alkyl group has from 1 to 4 carbon atoms, such as the methyl, ethyl, propyl, 2-propyl, 2-methyl-2-propyl, 2-methylpropyl, butyl and 2-butyl esters are most preferred. There is no particular restriction upon the nature of such salts and esters, provided that, where they are intended for therapeutic use, they should be "pharmaceutically acceptable", which, as is well known to those skilled in the art, means that they should not have a reduced activity (or unacceptably reduced activity) or an increased toxicity (or unacceptably increased toxicity) as compared with the free acids. Where the compounds are intended for non-therapeutic use, for example as intermediates in the preparation of other compounds, even these restrictions do not apply.

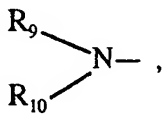
Now, referring to formula (II), the alkyl group R_8 may be a straight-chain or branched alkyl of 1 to 10 carbon atoms, such as methyl, ethyl, propyl, 2-propyl, 2-methylpropyl, 2-methyl-2-propyl, butyl, 2-butyl, pentyl, hexyl, octyl, decyl; the cycloalkyl group R_8 may be a cycloalkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl; and the phenylalkyl group R_8 may be a phenylalkyl group of 7 to 11 carbon atoms such as benzyl and phenethyl. As examples of the heterocyclic group R_8 may be mentioned 5- or 6- membered

groups each including 1 or 2 heteroatoms selected from among nitrogen, oxygen and sulfur, such as pyridyl, thienyl, furyl, thiazolyl, etc. When R_8 is



the alkyls R_9 and R_{10} may each be a alkyl of 1 to 4 carbon atoms, such as methyl, ethyl, propyl, 2-propyl and butyl or may be an aralkyl group, such as benzyl or phenethyl or a heterocyclyl group, such as pyridyl, thienyl, furyl or a condensed heterocyclic ring such as indolyl or benzoxazolyl. When R_9 and R_{10} are combined to each other to form a 5- or 6-membered heterocyclic group as taken together with the adjacent N atom, this heterocyclic group may further include a heteroatom selected from among nitrogen, oxygen and sulfur, as exemplified by piperidino, morpholino, pyrrolidino and piperazino. The lower alkylene group R_7 may contain 1 to 3 carbon atoms and, thus, may for example be methylene, ethylene or trimethylene, optionally substituted by C_1-C_4 alkyl or hydroxy groups.

As examples of the alkyls L_1 and L_2, there may be mentioned lower alkyl groups of 1 to 3 carbon atoms, such as methyl and ethyl. The alkylene group formed as L_1 and L_2 are joined together is a alicyclic group with from 2 to 6 carbon atoms, such as cyclopropyl, cyclopentyl and cyclohexyl. The cycloalkyl, phenylalkyl, phenyl and heterocyclic groups mentioned above, as well as said heterocyclic group derived from



may have 1 to 3 substituents in optional positions on the respective rings. As examples of such substituents may be mentioned lower alkyls (e.g. methyl, ethyl,

etc.), lower alkoxy groups (e.g. methoxy, ethoxy, etc.), halogens (e.g. fluorine, chlorine, bromine, etc.), oxo, hydroxyl and its acyl derivatives. The case also falls within the scope of the formulae (II) and (III) that an alkylenedioxy group of the formula -O-(CH_2)k-O- [k is an integer from 1 to 3], such as methylenedioxy, is attached to the two adjacent carbon atoms on the ring to form an additional ring.

Illustrative examples of compounds comprising thiazolidines and oxazolidines derived from formulae (II) and (III) of this invention include:

5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione,

5-[4-(t-3-hydroxy-1-methyl-r-1-cyclohexylmethoxy)benzyl]thiazolidine-2,4-dione,

5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(3-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(2-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(4-methyl-5-thiazolyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(2-thienyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-[4-(2-morpholinoethoxy)benzyl] thiazolidine-2,4-dione,

5-{4-[2-(2-di-n-butylamino)ethoxy]benzyl}thiazolidine-2,4-dione,

5-[(2-benzyl-3,4-dihydro-2H-benzopyran-6-yl)methyl]thiazolidine-2,4-dione,

5-[(2-benzyl-3,4-dihydro-2H-benzopyran-6-yl)methylene]thiazolidine-2,4-dione,

5-[(2-benzyl-2,3-dihydrobenzothiophene-5-yl)methyl]thiazolidine-2,4-dione,

5-[(2-benzyl-2,3-dihydro-1,1-dioxobenzothiophene-5-yl)methyl]thiazolidine-2,4-dione,

5-{4-[2-hydroxy-2-(5-ethyl-2-pyridyl)ethoxy)benzyl}thiazolidine-2,4-dione,

5-{4-[2-hydroxy-2-(6-methyl-2-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl}thiazolidine-2,4-dione[1], and

5-{4-[2-[N-(benzoxazol-2-yl)-N-methylamino]ethoxy]benzyl}oxazolidine-2,4-dione.

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[1] rosiglitazone

Referring to formula (IV), illustrative examples of compounds comprising thiazolidine and oxazolidine derivatives of this invention include:

5-[4-(2-phenyl-4-oxazolylmethoxy)benzyl]thiazolidine-2,4-dione,
5-[4-(2-phenyl-5-methyl-4-oxazolylmethoxy)benzyl]thiazolidine-2,4-dione,
5-{4-[2-(2-phenyl-5-hydroxymethyl-4-oxazolyl)methoxy]benzyl}thiazolidine-2,4-dione,
5-{4-[3-(2-phenyl-5-methyl-4-oxazolyl)propylthio]benzyl}thiazolidine-2,4-dione,
5-{4-[3-(2-phenyl-5-methyl-4-oxazolyl)propionyl]benzyl}thiazolidine-2,4-dione,
5-{[4-[3-(2-phenyl-5-methyl-4-oxazolyl)propionyl]-2-thienyl]methyl}thiazolidine-2,4-dione,
5-{[4-[1-hydroxy-3-(2-phenyl-5-methyl-4-oxazolyl)propyl]-2-pyridyl]methyl}thiazolidine-2,4-dione,
5-{4-[2-(2-phenyl-5-methyl-4-oxazolyl)-2-hydroxyethoxy]benzyl} thiazolidine-2,4-dione, and
5-[2-(2-phenyl-5-methyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]oxazolidine-2,4-dione.

Referring to formula (V), illustrative examples of compounds comprising thiazolidine and oxazolidine derivatives include:

5-{4-[2-(5-methyl-4-phenyl-2-oxazolyl)ethoxy]benzyl}thiazolidine-2,4-dione,
5-{4-[2-(4-cyclohexyl-5-methyl-2-oxazolyl)ethoxy]benzyl}thiazolidine-2,4-dione,
5-{4-[2-(4-isobutyl-5-methyl-2-oxazolyl)ethoxy]benzyl}thiazolidine-2,4-dione, and
5-[4-(4-phenyl-2-thiazolylmethoxy)benzyl]thiazolidine-2,4-dione.

Referring to formulae (VIa), (VIb), (VIc) and (VId), illustrative examples of compounds comprising thiazolidine and oxazolidine derivatives include:

(-)-5-{4-[[1-(2-benzothiazolyl)-(2S)-2-pyrrolidinyl]methoxy]benzyl}thiazolidine-2,4-dione,
5-{4-[2-(2-naphthyl)ethoxy]benzylidene}thiazolidine-2,4-dione,

5-[4(2-isopropylbenzoxazol-5-ylmethoxy)benzyl]thiazolidine-2,4-dione, and
5-[4(2-cyclohexyl-7-methoxybenzoxazol-5-ylmethoxy)benzyl]oxazolidine-2,4-dione.

Referring to formula VII, illustrative examples of compounds comprising thiazolidine and oxazolidine derivatives of this invention include:
5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl methoxy)benzyl]thiazolidine-2,4-dione,
5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-yl methoxy)benzyl]thiazolidine-2,4-dione,
5-[4-6-hydroxy-5,7-diisopropyl-2.methylchroman-2-yl methoxy)benzyl]thiazolidine-2,4-dione, and
5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl methoxy) benzyl] thiazolidine-2,4-dione.

Referring to formula VIII, illustrative examples of compounds comprising thiazolidine and oxazolidine derivatives of this invention include:
5-{4-[2-(5-(3-chlorophenyl)oxazolidin-2-on-3-yl)propyl]benzyl}thiazolidine-2,4-dione,
5-{4-[2-(5-(3-phenyl)oxazolidin-2-on-3-yl)ethoxy]benzyl}thiazolidine-2,4-dione,
5-{4-[2-(5-(3,5-dimethyl-4-hydroxyphenyl)oxazolidin-2-on-3-yl)propoxy]benzyl} thiazolidine-2,4-dione,
5-{4-[2-(5-(3-chlorophenyl)oxazolidin-2-thion-3-yl)propoxy]benzyl}thiazolidine-2,4-dione, and
3-methoxycarbonylmethyl-5-{4-[2-(5-(3-trifluorophenyl)oxazolidin-2-on-3-yl)1-methylethoxy] benzyl}thiazolidine-2,4-dione.

Referring to formula IX, illustrative examples of compounds comprising thiazolidine and oxazolidine derivatives of this invention include:
5-{4-[2-(N-(N^1-phenylthioureido)ethoxy)]benzyl}thiazolidine-2,4-dione, and
5-{4-[2-(N-methyl-N^1-phenylureido)ethoxy)]benzyl}thiazolidine-2,4-dione.

Referring to formula X, illustrative examples of compounds comprising thiazolidine and oxazolidine derivatives of this invention include:
5-{4-[2-(N-benzoyl-N-methylamino)ethoxy]benzylidene}thiazolidine-2,4-dione,
5-{4-[2-(N-(5-chloro-2-methoxybenzoyl)amino)ethoxy]benzyl}thiazolidine-2,4-dione,
5-{4-[2-(2,3-dihydro-1H-isoindol-1-on-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione, and
5-{4-[2-(N-methyl-N-(phenoxycarbonyl)amino)ethoxy]benzyl}thiazolidine-2,4-dione.

Referring to formula XI, illustrative examples of compounds comprising thiazolidine and oxazolidine derivatives of this invention include:
5-{4-[2-phenoxyethoxy]benzyl}thiazolidine-2,4-dione, and
5-{4-[2-(N-methyl-N-phenylamino)ethoxy]benzyl}thiazolidine-2,4-dione.

Where chiral centers are present, all stereoisomeric forms are intended. For example, the compounds of formula (VIII), wherein R is oxazolidin-2-one, possess a chiral center at the 5- position of the ring which can exist in R- or S-configuration. The expression "5RS racemic" refers to those compounds of formula (VIII) which are unresolved with reference to this specific chiral center, comprising equal parts of 5R and 5S isomers. The expression 5R optically active refers to those compoundsof formula (VIII) which have been resolved and have R stereochemistry at ring position 5.

The expression "pharmaceutically-acceptable cationic salts" is intended to define such salts as the alkali metal salts, (e.g. sodium, potassium or lithium), alkaline earth metal salts (e.g. calcium, barium or magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine,

piperazine, tromethamine (2-amino-2-hydroxymethyl- 1,3-propanediol), guanidine, aminoguanidine, dicyclohexylamine, procaine, and salts with a basic amino acid, such as lysine or arginine. An especially preferred such salt is the sodium salt. The expression "pharmaceutically-acceptable acid addition salts" is intended to include such salts as the hydrochloride, hydrobromide, hydroiodide, nitrate, hydrogen sulfate, dihydrogen phosphate, mesylate, maleate, succinate, etc.

The thiazolidine and oxazolidine derivatives of the present invention provide for a pharmaceutical and method for treatment of acute myocardial infarction. The active ingredient of the pharmaceutical are well-known compounds and are generally described as 5'-aryl substituted thiazolidine and oxazolidine derivatives (also commonly known as "glitazones"). These compounds are known to be useful for the treatment of diabetes and obesity associated hypertension.

The compounds generally fall into the family of compounds of formula I which is then subdivided into several genera. The following references, which are expressly incorporated by reference herein, disclose synthetic methods for the compounds of general formula I with the several descriptions (formulas II through XI) of substituent R: U.S. Pat. Nos. 4,486,594, 4,461,902 and 4,444,779 issued to Kawamatsu et.al.; U.S. Pat. Nos. 4,812,570 and 4,687,777 issued to Meguro et.al.; U.S. Pat. No. 4,791,125 issued to Clark; U.S. Pat. Nos. 4,738,972 and 4,703,052 issued to Eggler et.al. et.al. and Cantello et.al., J Med Chem 37:3977-3985 (1994) describe the synthesis of compounds where R is represented by formulas II and III. When R is represented by formula IV the synthetic methods are described in U.S. Pat. No. 5,498,621 issued to Dow; U.S. Pat. Nos. 5,330,998, 5,130,379 and 5,036,079 issued to Clark et.al.; and U.S. Pat. No. 4,725,610 issued to Meguro et.al.. When R is represented by formula V the synthetic methods are described in U.S. Pat. No. 5,266,582 issued to de Neuteuil et.al. and U.S. Pat. No. 4,775,687 issued to Meguro et.al. When R is represented by formulas VIa-VIc the synthetic

methods are described in U.S. Pat. No. 5,266,582 issued to de Nauteuil et. al. and when R is represented by formula VId the synthetic methods are described in U.S. Pat. No. 5,037,842 issued to Goldstein. The synthetic methods for compounds where R is represented by formula VII are described in U.S. Pat. No. 5,614,542 issued to Horikoshi et.al. and U.S. Pat. Nos. 4,873,255 and 4,572,912 issued to Yoshioka et.al. When R is represented by formula VIII the synthetic methods are described in U.S. Pat. No. 5,436,257 issued to Fujita et.al. and U.S. Pat. No. 4,968,707 issued to Clark et.al., whereas when R is represented by formula IX the synthetic methods are described in U.S. Pat. No. 4,918,091 issued to Cantello et.al. The synthetic methods for the preparation of thiazolidine-2,4-dione nucleus, in addition to the patent references cited above, have been described in U.S. Pat. No. 5,053,420 issued to Pershadsingh et.al. and synthesis of oxazolidine-2,4-dione nucleus has been described in U.S. Pat. No. 4,430,337 issued to Holland, U.S. Pat. No. 5,498,621 issued to Dow et.al. and U.S. Pat. Nos. 5,688,823 and 5,578,620 issued to Fujita et. al. When R is represented by formula X the synthetic methods are described in U.S. Pat. No. 5,478,851 and when R is represented by formula XI the synthetic methods are described in U.S. Pat. No. 5,132,317.

The thiazolidine- and oxazolidine-2,4-diones of the present invention are clinically administered to mammals, including humans, via either the oral, sublingual, rectal, vaginal, nasal, transdermal, subcutaneous, intramuscular, pulmonary or the intravenous route. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication, or absorption following oral administration is impaired or slow to reach therapeutically efficacious levels, as by disease or other abnormality, it is essential that the drug be administered parenterally. The dosage forms and modes of administration described herein are also useful for carrying out the method of the present invention. By either route, the dosage is in the range of about 0.10 to about 50 mg/kg body weight of

the subject per day, preferably about 0.10 to about 10 mg/kg body weight per day administered singly or as a divided dose. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter increments made to determine the most suitable dosage. This will vary according to the particular compound employed and with the subject being treated.

The compounds can be used in pharmaceutical preparations containing the compound, or pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described above. Thus, for oral administration the compounds can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parenteral administration the compounds can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically acceptable salts of the compounds. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans. The transdermal route may include passive diffusion from a topical formulation such as a cream or a gel or a transdermal patch or active diffusion such as electro-assisted delivery including iontophoresis, phonophoresis and electroporation. The compounds may be delivered as a solution or as a powder using pressurized devices known in the art, for example, Mediject and Powderject.

The present invention is illustrated by the following examples. However, it should be understood that the invention is not limited to the specific details of these examples.

EXAMPLE 1

The effect of (+)-5-{4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]benzyl}thiazolidine-2,4-dione (troglitazone) on programmed cell death (apoptosis) of cardiac muscle cells was tested with in situ terminal deoxynucleotidyl transferase assay. Primary cardiomyocytes were maintained in regular growth medium containing 10% fetal bovine serum. Apoptosis of cardiomyocytes was induced with serum withdrawal and addition of doxorubicin. Five μm of (+)-5-{4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran -2-yl)methoxy] benzyl}thiazolidine-2,4-dione (troglitazone), when added to the culture medium, reduced apoptosis of cardiomyocytes by approximately 60%. Apoptosis of cardiomyocytes was determined with TUNEL assay (Wang L et. al., Endocrinology 1998 Mar, 139(3): 1354-1360). The results clearly show that therapeutic concentrations of (+)-5-{4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy] benzyl} thiazolidine-2,4-dione (troglitazone) significantly inhibits apoptosis of cardiac muscle cells in culture.

EXAMPLE 2
Tablets

A tablet base is prepared by blending the following ingredients in the proportion by weight indicated:

Sucrose, U.S.P.	80.3
Topioca starch	13.2

Magnesium stearate 6.5

Into this tablet base there is blended sufficient sodium dl-5-[(2-benzyl-3,4-dihydro-2H-benzopyran-6-yl)methyl]thiazolidine-2,4-dione to form tablets containing 50 mg, 100 mg or 250 mg of active drug (weight equivalent to the free acid). The portion of blend to active drug is within the limits of 1-0.167 to 1-1, e.g., in the extremes, 62.0 mg of sodium salt dihydrate and 300 mg of blend in a 50 mg tablet or 310.0 mg of sodium salt dihydrate and 250 mg of blend in a 250 mg tablet.

EXAMPLE 3

The experiment of Example 1 was repeated replacing sodium dl-5-[(2-benzyl-3,4-dihydro-2H-benzopyran-6-yl)methyl]thiazolidine-2,4-dione with the appropriate salt of one of the following active ingredients:

dl-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl methoxy)benzyl]thiazolidine-2,4-dione,

5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione,

5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(2-phenyl-5-methyl-4-oxazolyl)-2-hydroxyethoxy]benzyl} thiazolidine-2,4-dione, or

5-{4-[3-(2-phenyl-5-methyl-4-oxazolyl)propionyl]benzyl}thiazolidine-2,4-dione. The results on apoptosis were essentially as reported in Example 1.

EXAMPLE 4
Injectable Preparation

Sterile sodium d-5-[(2-benzyl-3,4-dihydro-2H-benzopyran-6-yl)methyl] thiazolidine-2,4-dione was dry filled into vials so as to contain 571.0 mg of the sodium salt per vial (equivalent to 550 mg of free acid). Prior to use, sterile water

for injection (11 ml) is added, and the mixture shaken to form a solution, containing 50 mg/ml of active drug, which is suitable for intravenous, intramuscular or subcutaneous injection. Alternatively, vials were filled by a freeze drying procedure. Two ml of a sterile, aqueous solution containing 286 mg/ml of sodium salt is introduced into each vial. The vials are freeze dried on trays.

EXAMPLE 5

Example 1 was repeated replacing sodium dl-5-[(2-benzyl-3,4-dihydro-2H-benzopyran-6-yl)methyl]thiazolidine-2,4-dione with the appropriate salt of one of the following active ingredients:

dl-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl methoxy)benzyl]thiazolidine-2,4-dione,

5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione,

5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(2-phenyl-5-methyl-4-oxazolyl)-2-hydroxyethoxy]benzyl} thiazolidine-2,4-dione, or

5-{4-[3-(2-phenyl-5-methyl-4-oxazolyl)propionyl]benzyl}thiazolidine-2,4-dione.

Again, the apoptosis measurements were similar to those presented in Example 1.

EXAMPLE 6

As antidiabetic agents glitazones appear to function by amplifying the metabolic actions of both insulin and IGF1 (insulin-like growth factor) through post-receptor level activation of PPARγ receptors. The apoptosis experiments on cardiomyocytes were repeated using either serum withdrawal (SW) or administration of doxorubicin to induce apoptosis. As earlier cell death was measured fluorescently with the TUNEL assay. SW and 0.5 μM doxorubicin

increased the number of TUNEL positive (apoptotic) cells three fold. Addition of 5 μM toglitazone reduced the TUNEL positive cells by 50%. Addition of IGF1 at 10^{-8}M decreased the number of TUNEL positive cells by 60%. Significantly, IGF1 and troglitazone showed an additive or synergistic effect. Treatment with both of these agents suppressed the TUNEL positive cells to control levels.

Experiments were undertaken to evaluate the effects of troglitizone on apoptotic signaling through the Caspase 3 pathway. SW and doxorubicin treatment increased Caspase 3 levels 4-5 fold. Neither troglitizone nor IGF1 alone altered the activation of Caspase 3. Therefore, these agents suppress apoptosis through pathways independent of Caspase 3. However, troglitizone was seen to suppress SW and doxorubicin activation of PARP, a distal step of apoptotic signaling.

The experimental results also show that troglitazone and/or ciglitizone activate MAP (mitogen activated protein) kinase and PI3 kinase (phosphotidyl inositol 3' kinase) which signaling molecules have both been implicated in preventing apoptosis of cardiomyocytes (see Parrizasm, Saltiel, and LeRoith, J. Biological Chemistry, 272:154-61 (1997)). These results occur at the same concentration levels at which these agents are typically administered *in vivo* for antidiabetic therapies. Therefore, there is great potential for using glitazones in the treatment of myocardial infarctions. The observed kinetics of myocyte apoptosis confirm that the therapeutic administration should begin immediately upon infarct.

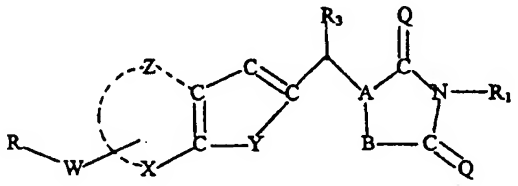
In addition to the equivalents of the claimed elements, obvious substitutions now or later known to one with ordinary skill in the art are defined to be within the scope of the defined elements. The claims are thus to be understood to include what is specifically illustrated and described above, what is conceptually equivalent, what can be obviously substituted and also what essentially incorporates the essential idea of the invention. Those skilled in the art will appreciate that various adaptations and modifications of the just-described preferred embodiment can be configured without

departing from the scope and spirit of the invention. The illustrated embodiment has been set forth only for the purposes of example and that should not be taken as limiting the invention. Therefore, it is to be understood that, within the scope of the appended claims, the invention may be practiced other than as specifically described herein.

CLAIMS

I Claim:

1. A method for the improvement of myocardial remodeling and cardiac function after acute myocardial infarction which comprises administering a therapeutically effective amount of a compound selected from the group consisting of thiazolidine and oxazolidine derivatives having the formula (I),



wherein,

Q is selected from O (oxo) or NOR_2 (imino), where R_2 is independently selected from hydrogen, alkyl, cycloalkyl, or acyl,

R_1 is selected from hydrogen, alkyl, cycloalkyl, alkoxycarbonyl, or carboxyalkyl and their ester derivatives,

R_3 is selected from hydrogen, alkyl or cycloalkyl,

B is selected from O (oxa) or S (thia),

A is selected from N or CR_4, where R_4 is hydrogen, cycloalkyl or alkyl and where R_3 and R_4 may combine to form a cyclic ring, or a double covalent bond,

Y is selected fromCH=CH, N=CH, CH=N, S, O or NR_5, where R_5 is selected from hydrogen, cycloalkyl or alkyl,

X is selected from O (oxa), C=O (carbonyl), CHOH, CH_2, $C=NOR_2$, S, SO, SO_2, SO_2NR_5, R_5NSO_2, $CONR_5$ or

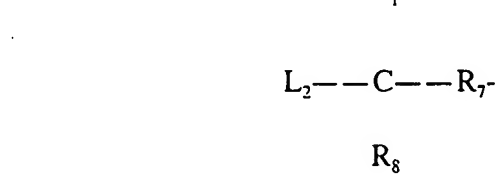
NR_5CO, where R_5 is selected from hydrogen, cycloalkyl or alkyl,

Z is selected from CH=CH, CH=N, $-(CH_2)nO-$ or $(CH_2)n$, where n is 0-3,

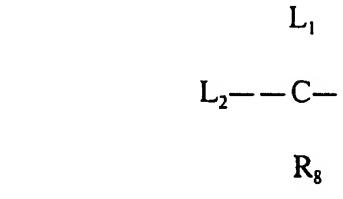
W is selected from $(CH-R_6)m$, where m is 0-4, R_6 is selected from hydrogen, alkyl, cycloalkyl, hydroxy, $(CH_2)nOH$ and their acyl derivatives and n is 1-3; or W is selected from a 5- or 6-membered saturated nitrogen heterocycle wherein methylene hydrogens are optionally substituted by alkyl and hydroxy groups and an R group is attached to a nitrogen heteroatom; and

wherein R is selected from the group consisting of

Formula (II)

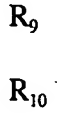


, Formula (III)



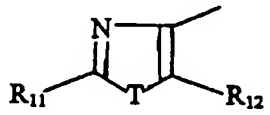
wherein R_8 is selected from alkyl, cycloalkyl, aralkyl, aryl, a five- to ten-membered heterocyclic group including one or two heteroatoms selected from

the group consisting of nitrogen, oxygen and sulfur, or a group of the formula



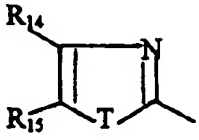
where R_9 and R_{10} are selected from alkyl, aralkyl or heterocyclyl or R_9 and R_{10} are combined to each other either directly or as interrupted by a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur to form a five- or six-membered ring; R_7 is a bond or lower alkylene group; L_1 and L_2 are lower alkyl or L_1 and L_2 are combined to each other to form an alkylene group , provided that when R_8 is other than alkyl, L_1 and L_2 may further be hydrogen,

Formula (IV)



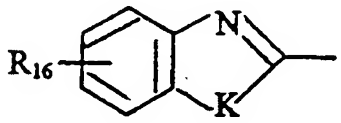
wherein T is selected from O, S or NR_{13}; R_{13} is selected from hydrogen or alkyl; R_{11} is selected from hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl or mono- or disubstituted aryl; R_{12} is selected from hydrogen and an alkyl group,

Formula (V)



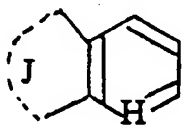
wherein T is selected from O, S and NR_{13}; R_{14} and R_{15} each independently is selected from hydrogen, cycloalkyl, alkyl, aryl, aralkyl and a heterocyclic residue or R_{14} and R_{15} form a condensed ring with an oxazole, thiazole or imidazole ring,

Formula (VIa)



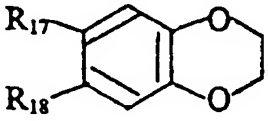
wherein K is selected from a S, O or NH;and R_{16} is selected from hydrogen, a halogen atom, an alkyl, an alkoxy, haloalkyl and cyano group,

Formula (VIb)



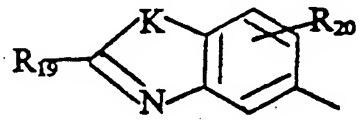
wherein J represents a ring with 5 or 6 members and H' is selected from CH or N,

Formula (VIc)



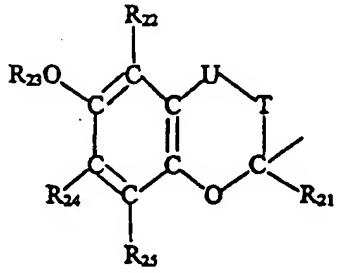
wherein R_{17} and R_{18} are selected from hydrogen, halogen atom, alkyl group, alkoxy group, or together form with the carbon atoms to which they are attached a saturated ring with 5 or 6 members which may optionally contain 1 or 2 oxygen atoms,

Formula (VId)



wherein R_{19} is selected from alkyl, cycloalkyl, heterocyclyl, aryl and substituted aryl with one or more substituents; R_{20} is hydrogen, alkyl, alkoxy, halogen and K is as defined above for structure (VIa),

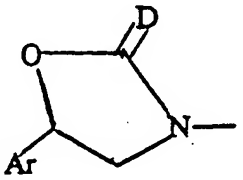
Formula (VII)



wherein R_{21} and R_{22} are selected from hydrogen and alkyl; R_{23} is selected from hydrogen, alkyl, an acyl group, an alkoxycarbonyl group and an aralkyloxycarbonyl group; R_{24} and R_{25} are selected from hydrogen, alkyl or alkoxy or R_{24} and R_{25}

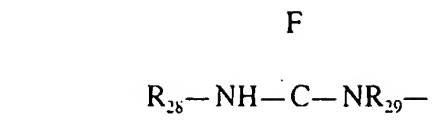
together represent an alkylenedioxy group, wherein the alkylene portion is methylene and ethylene; U is selected from a methylene group, a carbonyl group, a group of formula >CH-OR_{26}, or a group of formula >C=N-OR_{27}, where R_{27} represents hydrogen or alkyl; T represents a single bond or a methylene group; or when U represents a carbonyl group or said group of formula >C=N-OR_{27}, T, R_{21} and the carbon atom to which R_{21} is attached may together represent a group of formula -CH=C<, or U-T may represent a carbon-carbon double bond,

Formula (VIII)



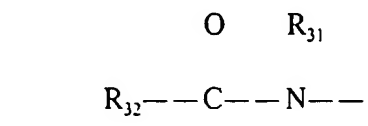
wherein D is O or S; Ar represents an unsubstituted aryl group having from 4 to 10 ring carbon atoms or a substituted aryl group which has from 4 to 10 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents selected from the group consisting of: halogen atoms; haloalkyl groups, in which the alkyl part has from 1 to 4 carbon atoms; hydroxy groups; acyloxy groups, in which the alkyl part has from 1 to 4 carbon atoms; alkyl groups having from 1 to 4 carbon atoms; and alkoxy groups having from 1 to 4 carbon atoms,

Formula (IX)



wherein, R_{28} represents an alkyl group or a substituted or unsubstituted aryl group; R_{29} represents hydrogen or alkyl; and F represents oxygen, sulfur or a moiety NR_{30} wherein R_{30} represents hydrogen or alkyl,

Formula (X)



wherein, R_{31} is a hydrogen atom, an alkyl group, an aralkyl group; R_{32} represents an alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aryloxy group, an aralkyl group, an aralkyl group wherein the alkylene or aryl moiety may be substituted or unsubstituted or a substituted or unsubstituted aromatic heterocyclyl group; or R_{31} together with R_{32} represents substituted or unsubstituted C_{3-4} polymethylene group, optional substituents for the polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group,

Formula (XI)

$$R_{33}--P-$$

wherein, R_{33} represents a substituted or unsubstituted aryl group; P represents O, S, NR_{34} wherein R_{34} represents a hydrogen atom, an alkyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group, and

pharmaceutically acceptable salts thereof.

2. The method of Claim 1; further comprising administration of a pharmaceutically acceptable excipient, diluent, or carrier.

3. A method of Claim 1, wherein,

Q is an oxygen atom;

B is a sulfur atom;

R_1 and R_3 are hydrogens;

A is -CH-, CR_4, and CR_4 and CHR_3 combine to form a doublebond, $-CR_3=C-$;

Y is CH=CH, N=CH or a sulfur atom;

Z is $(CH_2)n$, CH=CH or "no bond" and n is 1-3;

X is oxygen, sulfur, SO_2, a carbonyl or a CHOH group; and

W is $(CHR_6)m$, where m is 0-4, R_6 is hydrogen or hydroxy.

4. The method of Claim 1, wherein R is represented by Formula II, R_7 is a bond, R_8 is phenyl, thienyl, pyridyl or thiazolyl, substituted with lower alkyl and L_1 and L_2 are hydrogen atoms or R_8 is NR_9R_{10} where R_9 and R_{10} are alkyl, aralkyl or heterocyclyl or they may combine to form a heterocycle.

5. The method of Claim 1 wherein R is represented by Formula II, wherein R_8 is alkyl and L_1 and L_2 are combined to form a cycloalkyl group.

6. The method of Claim 1 wherein the compound is 5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione, also known as ciglitazone.

7. The method of Claim 1 wherein the compound is 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione, also known as pioglitazone.

8. The method of Claim 1 wherein the compound is 5-[(2-benzyl-3,4-dihydro-2H-benzopyran-6-yl)methyl]thiazolidine-2,4-dione, also known as englitazone.

9. The method of Claim 1 wherein the compound is 5-{[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl}thiazolidine-2,4-dione, also known as rosiglitazone.

10. The method of Claim 1 wherein R is represented by Formula IV, wherein R_{11} is hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl or mono- or disubstituted aryl with the same or different groups which are alkyl, alkoxy, haloalkyl, hydroxy, acyloxy or halogens and R_{12} is hydrogen or an alkyl group which may be substituted by a hydroxy or acyloxy group.

11. The method of Claim 1, wherein the compound is 5-{4-[3-(2-phenyl-5-methyl-4-oxazolyl)propionyl]benzyl}thiazolidine-2,4-dione, also known as darglitazone.

12. The method of Claim 1 wherein R is represented by Formula VII, wherein R_{21} and R_{22} represent hydrogen or alkyl groups;

R_{23} represents hydrogen, alkyl, an acyl group, alkoxycarbonyl group or an aralkyloxycarbonyl group;

R_{24} and R_{25} represent hydrogen, alkyl or alkoxy or R_{24} and R_{25} together represent an alkylenedioxy group, wherein the alkylene portion is methylene and ethylene;

U represents a methylene group, a carbonyl group, a group of formula >CH-OR_{26}, where R_{26} represents any one of the atoms or groups defined for R_{23}, or a group of formula >C=N-OR_{27}, where R_{27} represents hydrogen or alkyl;

T represents a single bond or a methylene group; or when U represents a carbonyl group or said group of formula >C=N-OR_{27}, T, R_{21} and the carbon atom to which R_{21} is attached form a group of formula -CH=C<; or U-T forms a carbon-carbon double bond.

13. The method of Claim 1 wherein the compound is (+)- 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, also known as troglitazone.

14. The method of Claim 1 wherein the compound is 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl methoxy)benzyl]thiazolidine-2,4-dione.

15. A method of treating myocardial infarction comprising administering a therapeutically effective amount of a compound selected from the group consisting of 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl methoxy)benzyl]thiazolidine-2,4-dione, (+)- 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, 5-{4-[3-(2-phenyl-5-methyl-4-oxazolyl)propionyl]benzyl}thiazolidine-2,4-dione, 5-{[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl}thiazolidine-2,4-dione, 5-[(2-benzyl-3,4-dihydro-2H-benzopyran-6-yl)methyl]thiazolidine-2,4-dione, 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione, and 5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione.

16. A method for the improvement of myocardial remodeling and cardiac function after acute myocardial infarction in a mammal, which may be human, comprising administering to said mammal suffering therefrom a therapeutically effective amount of a compound selected from the group consisting of

5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione,

5-[4-(t-3-hydroxy-1-methyl-r-1-cyclohexylmethoxy)benzyl]thiazolidine-2,4-dione,

5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(3-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(2-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(4-methyl-5-thiazolyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(2-thienyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-[4-(2-morpholinoethoxy)benzyl] thiazolidine-2,4-dione,

5-{4-[2-(2-di-n-butylamino)ethoxy]benzyl}thiazolidine-2,4-dione,

5-[(2-benzyl-3,4-dihydro-2H-benzopyran-6-yl)methyl]thiazolidine-2,4-dione,

5-[(2-benzyl-3,4-dihydro-2H-benzopyran-6-yl)methylene]thiazolidine-2,4-dione,

5-[(2-benzyl-2,3-dihydrobenzothiophene-5-yl)methyl]thiazolidine-2,4-dione,

5-[(2-benzyl-2,3-dihydro-1,1-dioxobenzothiophene-5-yl)methyl]thiazolidine-2,4-dione,

5-{4-[2-hydroxy-2-(5-ethyl-2-pyridyl)ethoxy)benzyl}thiazolidine-2,4-dione,

5-{4-[2-hydroxy-2-(6-methyl-2-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl}thiazolidine-2,4-dione

5-{4-[2-[N-(benzoxazol-2-yl)-N-methylamino]ethoxy]benzyl}oxazolidine-2,4-dione,

5-[4-(2-phenyl-4-oxazolylmethoxy)benzyl]thiazolidine-2,4-dione,

5-[4-(2-phenyl-5-methyl-4-oxazolylmethoxy)benzyl]thiazolidine-2,4-dione,

5-{4-[2-(2-phenyl-5-hydroxymethyl-4-oxazolyl)methoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[3-(2-phenyl-5-methyl-4-oxazolyl)propylthio]benzyl}thiazolidine-2,4-dione,

5-{4-[3-(2-phenyl-5-methyl-4-oxazolyl)propionyl]benzyl}thiazolidine-2,4-dione,
5-{[4-[3-(2-phenyl-5-methyl-4-oxazolyl)propionyl]-2-thienyl]methyl}thiazolidine-2,4-dione,
5-{[4-[1-hydroxy-3-(2-phenyl-5-methyl-4-oxazolyl)propyl]-2-pyridyl]methyl}thiazolidine-2,4-dione,
5-{4-[2-(2-phenyl-5-methyl-4-oxazolyl)-2-hydroxyethoxy]benzyl} thiazolidine-2,4-dione,
5-[2-(2-phenyl-5-methyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]oxazolidine-2,4-dione,
5-{4-[2-(5-methyl-4-phenyl-2-oxazolyl)ethoxy]benzyl}thiazolidine-2,4-dione,
5-{4-[2-(4-cyclohexyl-5-methyl-2-oxazolyl)ethoxy]benzyl}thiazolidine-2,4-dione,
5-{4-[2-(4-isobutyl-5-methyl-2-oxazolyl)ethoxy]benzyl}thiazolidine-2,4-dione,
5-[4-(4-phenyl-2-thiazolylmethoxy)benzyl]thiazolidine-2,4-dione,
(-)-5-{4-[[1-(2-benzothiazolyl)-(2S)-2-pyrrolidinyl]methoxy]benzyl}thiazolidine-2,4-dione,
5-{4-[2-(2-naphthyl)ethoxy]benzylidene}thiazolidine-2,4-dione,
5-[4(2-isopropylbenzoxazol-5-ylmethoxy)benzyl]thiazolidine-2,4-dione,
5-[4(2-cyclohexyl-7-methoxybenzoxazol-5-ylmethoxy)benzyl]oxazolidine-2,4-dione,
(+)-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl methoxy) benzyl] thiazolidine-2,4-dione,
5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-yl methoxy)benzyl]thiazolidine-2,4-dione,
5-[4-6-hydroxy-5,7-diisopropyl-2.methylchroman-2-yl methoxy)benzyl]thiazolidine-2,4-dione,
5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl methoxy)benzyl] thiazolidine-2,4-dione,

5-{4-[2-(5-(3-chlorophenyl)oxazolidin-2-on-3-yl)propyl]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(5-(3-phenyl)oxazolidin-2-on-3-yl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(5-(3,5-dimethyl-4-hydroxyphenyl)oxazolidin-2-on-3-yl)propoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(5-(3-chlorophenyl)oxazolidin-2-thion-3-yl)propoxy]benzyl}thiazolidine-2,4-dione,

3-methoxycarbonylmethyl-5-{4-[2-(5-(3-trifluorophenyl)oxazolidin-2-on-3-yl)1-methylethoxy] benzyl}thiazolidine-2,4-dione,

5-{4-[2-(N-(N^1-phenylthioureido)ethoxy)]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(N-methyl-N^1-phenylureido)ethoxy)]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(N-benzoyl-N-methylamino)ethoxy]benzylidene}thiazolidine-2,4-dione,

5-{4-[2-(N-(5-chloro-2-methoxybenzoyl)amino)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(2,3-dihydro-1H-isoindol-1-on-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-(N-methyl-N-(phenoxycarbonyl)amino)ethoxy]benzyl}thiazolidine-2,4-dione,

5-{4-[2-phenoxyethoxy]benzyl}thiazolidine-2,4-dione, and

5-{4-[2-(N-methyl-N-phenylamino)ethoxy]benzyl}thiazolidine-2,4-dione

17. The method of Claim 1, 15 or 16 further comprising administering a therapeutically effective amount of Insulin-like Growth Factor 1 (IGF1).

18. A method of treating myocardial infarction comprising administering a therapeutically effective amount of Insulin-like Growth Factor 1 (IGF1) together with a therapeutically effective amount of a compound selected from the group consisting of 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl methoxy)benzyl]thiazolidine-2,4-dione, (+)- 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, 5-{4-[3-(2-phenyl-5-methyl-4-oxazolyl)propionyl]benzyl}thiazolidine-2,4-dione, 5-{[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl}thiazolidine-2,4-dione, 5-[(2-benzyl-3,4-dihydro-2H-benzopyran-6-yl)methyl]thiazolidine-2,4-dione, 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione, and 5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/11101

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/425, 31/41, 31/42, 31/44

US CL :514/183, 252, 256, 337, 342, 360, 349, 456

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/183, 252, 256, 337, 342, 360, 349, 456

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,708,012 A (OLEFSKY) 13 January 1998.	1-18
A	US 5,602,133 A (ANTONUCCI et al.) 11 February 1997.	1-18
A	US 5,478,851 A (CANTELLO et al.) 26 December 1995.	1-18
A	US 5,441,971 A (SOHDA et al.) 15 August 1995.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
01 JULY 1999	20 JUL 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer RAYMOND J. HENLEY III
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